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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Frederick Hall et al.
Serial No. : 09/624,874
Filed : July 21, 2000
Title : MATRIX-TARGETED FUSION POLYPEPTIDES FOR TISSUE REGENERATION AND WOUND HEALING

Art Unit : 1647
Examiner : R. DeBerry

BOX SEQUENCE
Commissioner for Patents
Washington, D.C. 20231

VERIFIED STATEMENT UNDER 37 CFR §1.821(f)

I, Katica Magovcevic, declare that I personally prepared the paper and the computer-readable copy of the Sequence Listing filed herewith for the above-identified application and that the content of both is the same.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of The United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 8/21/01

K. Magovcevic

Katica Magovcevic

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CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

August 24, 2001
Date of Deposit

Lucille M. Bagalla
Signature

Lucille M. Bagalla
Typed or Printed Name of Person Signing Certificate

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE AND/OR AMINO ACID SEQUENCES

In response to the communication dated July 27, 2001 (copy enclosed), applicants submit herewith a Sequence Listing in computer readable form as required by 37 CFR §1.824. In addition, applicants submit an initial Sequence Listing as required under 37 CFR §1.823(a) and a statement under 37 CFR §1.821(f).

Applicants respectfully request entry of the paper copy and computer readable copy of the Sequence Listing filed herewith for the instant application. Furthermore, applicants request entry of the following amendments.

In the specification:

Insert the paper copy of the Sequence Listing filed herewith following the Oath/Declaration.

Replace the paragraph beginning at page 6, line 10, with the following rewritten paragraph:

--**Figure 1** is a diagram showing the structural domains of von Willebrand Factor. The A1 loop within the mature polypeptide encompasses the GP1b, collagen and heparin binding domains

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Lucille M. Begalla
Signature

Lucille M. Begalla
Typed or Printed Name of Person Signing Certificate

that function to promote platelet adhesion, collagen binding and heparin binding. The minimal collagen binding sequences of human and bovine vWF, including the flanking residues, are shown (SEQ ID NO:12).--

Replace the paragraph beginning at page 6, line 17, with the following rewritten paragraph:

--**Figure 2** is schematic diagram showing the design of recombinant EGF-CBD fusion proteins. Targeted congeners of epidermal growth factor consisting of a 6xHis purification tag, an auxiliary von Willebrand factor-derived collagen-binding domain, and the cDNA sequence encoding the mature active fragment of human EGF (EGF 53+7 flanking amino acids) are shown (P1 sequences are listed as SEQ ID NOs:2 and 3; P2 sequences are listed as SEQ ID NOs:4 through 6; P3 sequences are listed as SEQ ID NOs:7 and 8; P4 sequences are listed as SEQ ID NOs:9 through 11).--

Replace the paragraph beginning at page 39, line 5, with the following rewritten paragraph:

--**Molecular Engineering And Cloning Of The Expression Plasmids.** Figure 1 shows diagrammatically the structural domains of von Willebrand Factor (vWF), identifying the primary collagen-binding domain (CBD) within the A1 loop of the mature polypeptide. The mimimal collagen binding amino acid sequences of human and bovine vWF, including the flanking residues, are shown. The mature EGF polypeptide, consisting of 53 amino acids, is generated from a large transmembrane precursor protein by proteolytic cleavage (Figure 2). In engineering the EGF-CBD fusion proteins, human coding sequences of EGF, including two additional residues at the N-terminal end and 5 amino acids at the C-terminal end of the protein were utilized. This design not only retains the original (physiological) cleavage sites, but includes these native flanking residues in an effort to facilitate the renaturation of the recombinant protein. The extended C-terminal residues (H-A-G-H-G; SEQ ID NO:5), in particular, are considered to be important design considerations in that they are very similar to the N-terminal sequences flanking the native vWF CBD (see Figure 1). Therefore, this design is intended to optimize both the refolding of the recombinant fusion protein and the presentation of the

collagen-binding domain (CBD) in solution. Moreover, the retention of the natural proteolytic cleavage site between the growth factor and the intrinsic CBD are intended to provide a mechanism for enzymatic release (*i.e.*, "time release") of the soluble growth factor to enhance its physiological efficacy and potential therapeutic utility.--

REMARKS

Applicants hereby submit that the enclosures fulfill the requirements under 37 C.F.R. §1.821-1.825. The amendments in the specification merely insert the paper copy of the Sequence Listing and sequence identifiers in the specification. No new matter has been added.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment.

Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 8-24-01

Scott C. Harris
Reg. No. 32,030

Fish & Richardson P.C.
4350 La Jolla Village Drive, Suite 500
San Diego, CA 92122
Telephone: (858) 678-5070
Facsimile: (858) 678-5099

"Version With Markings to Show Changes Made"

In the specification:

Paragraph beginning at page 6, line 10, has been amended as follows:

Figure 1 is a diagram showing the structural domains of von Willebrand Factor. The A1 loop within the mature polypeptide encompasses the GP1b, collagen and heparin binding domains that function to promote platelet adhesion, collagen binding and heparin binding. The minimal collagen binding sequences of human and bovine vWF, including the flanking residues, are shown (SEQ ID NO:12).

Paragraph beginning at page 6, line 17, has been amended as follows:

Figure 2 is schematic diagram showing the design of recombinant EGF-CBD fusion proteins. Targeted congeners of epidermal growth factor consisting of a 6xHis purification tag, an auxiliary von Willebrand factor-derived collagen-binding domain, and the cDNA sequence encoding the mature active fragment of human EGF (EGF 53+7 flanking amino acids) are shown (P1 sequences are listed as SEQ ID NOs:2 and 3; P2 sequences are listed as SEQ ID NOs:4 through 6; P3 sequences are listed as SEQ ID NOs:7 and 8; P4 sequences are listed as SEQ ID NOs:9 through 11).

Paragraph beginning at page 39, line 5, has been amended as follows:

Molecular Engineering And Cloning Of The Expression Plasmids. Figure 1 shows diagrammatically the structural domains of von Willebrand Factor (vWF), identifying the primary collagen-binding domain (CBD) within the A1 loop of the mature polypeptide. The mimimal collagen binding amino acid sequences of human and bovine vWF, including the flanking residues, are shown. The mature EGF polypeptide, consisting of 53 amino acids, is generated from a large transmembrane precursor protein by proteolytic cleavage (Figure 2). In engineering the EGF-CBD fusion proteins, human coding sequences of EGF, including two additional residues at the N-terminal end and 5 amino acids at the C-terminal end of the protein were utilized. This design not only retains the original (physiological) cleavage sites, but

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STATEMENT UNDER 37 CFR §1.821(f) AND (g)

I hereby state, as required by 37 C.F.R. §1.821(f), that the content of the paper and computer-readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. §§1.821(c) and (e), respectively, are the same.

I hereby state, as required by 37 C.F.R. §1.821(g), that the enclosed submission includes no new matter.

Respectfully submitted,

Date: 8/24/01

Michael Reed, Ph.D.
Reg. No. 45,647

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Lucille M. Begalka
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